CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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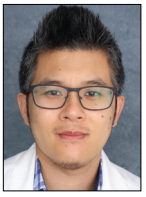
EGFR Inhibitor Rechallenge in Metastatic Colorectal Cancer



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H&O How often do patients with colorectal cancer (CRC) develop metastatic disease?

JG Most CRC patients present with stage 1, 2, or 3 disease, with only 20% to 25% of patients presenting with de novo metastatic disease. However, approximately half of patients who present with localized disease eventually develop metastatic disease. Given that CRC is the third most common cancer among men and women in the United States, CRC represents a high public burden of disease.

H&O What is the standard first-line treatment of metastatic CRC?

JG A subset of patients with oligometastatic disease can benefit from surgery or local therapies, including ablation or radiation therapy to the liver, for example, but most patients with metastatic CRC receive systemic therapy. Decisions regarding the optimal first-line treatment are based on the molecular profile of the cancer. For example, for the 5% of patients who have microsatellite instability (MSI)-high CRC, the optimal first-line treatment is usually immune checkpoint inhibition with pembrolizumab (Keytruda, Merck). Most patients, however, will have microsatellite-stable (MSS) cancer and will not be candidates for standard-of-care immunotherapy.

After MSI status, the next question is whether the primary tumor is left-sided or right-sided. For patients with a left-sided primary tumor that is *RAS/BRAF*–wild-type, standard first-line therapy is doublet chemotherapy plus an epidermal growth factor receptor (EGFR) inhibitor such as cetuximab (Erbitux, Lilly) or panitumumab (Vectibix, Amgen). For patients with a left-sided primary tumor that is *RAS/BRAF*-mutated, standard first-line therapy is doublet chemotherapy plus a biologic agent, most often a vascular endothelial growth factor (VEGF) inhibitor such as bevacizumab. For patients with a right-sided primary tumor, standard first-line therapy is a doublet plus VEGF inhibition, given the lack of benefit from adding EGFR inhibition to chemotherapy in this population. There is also the option of triplet chemotherapy in those who are deemed fit enough to tolerate such therapy.

H&O What is the standard second-line treatment for metastatic CRC?

JG For MSS metastatic CRC, we want to use whatever chemotherapy backbone we did not use in the first line. For example, in a patient with right-sided CRC, we might use leucovorin, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX) plus bevacizumab as first-line therapy, and leucovorin, 5-FU, and irinotecan (FOLFIRI) plus bevacizumab as second-line therapy.

We also have some additional options in the second line for patients who have a targetable mutation. For example, for patients with *BRAF*-mutated metastatic CRC, we have the option of encorafenib (Braftovi, Pfizer) plus cetuximab as second-line treatment; this combination has received US Food and Drug Administration (FDA) approval. For patients with *HER2* amplifications, we have FDA approval for tucatinib (Tukysa, Seagen) plus trastuzumab.

H&O What is the standard third-line treatment for metastatic CRC?

JG We have the option of rechallenging with FOLFOX in the third line. Thanks to the recent results of the phase 3 SUNLIGHT trial, we also have phase 3 evidence that trifluridine and tipiracil (Lonsurf, Taiho Oncology) plus bevacizumab is a standard third-line option.[1] And of course, we prioritize clinical trials through all lines of treatment.

H&O What is the rationale behind EGFR inhibitor rechallenge?

JG Historically, patients needed to have wild-type *RAS* or *BRAF* status to be candidates for EGFR inhibition. If we started a patient on first-line chemotherapy plus an anti-EGFR agent and the cancer progressed on this combination, studies showed that the disease had developed resistance to anti-EGFR agents, based on either a primary or acquired mutation. These mutations can occur within the EGFR extracellular domain. Some patients will also develop resistance through the emergence of *RAS*, *BRAF*, *HER2*, *PIK3*, *MET,* and *MAP2K1* mutations. Fortunately, the resistance clones tend to decay over time—data show that this process can occur at a median of 4 months. We cannot withhold treatment for 4 months in a patient with metastatic disease, but we can certainly use a different therapy as a second-line treatment and return to EGFR inhibition in the third line. Another advantage of waiting is that the second-line therapy has the potential to eliminate resistant clones, even as they are decaying over time. By the time patients need third-line treatment, many of them will be able to respond like *RAS/BRAF*–wild-type patients.

H&O How often does rechallenge with EGFR inhibitors lead to a durable response?

JG We have only limited data on this, mostly from single-arm, phase 2 studies, but what we have seen with anti-EGFR rechallenge is response rates ranging from 20% to 50%. The median progression-free survival (PFS) is usually between 2 and 6 months.

One of the first of these studies was the CRICKET study, which enrolled patients with *RAS*–wild-type mCRC.[2] Patients received first-line therapy with a chemotherapy doublet plus cetuximab, and those who experienced progression received second-line therapy without an anti-EGFR agent. Third-line therapy consisted of irinotecan plus cetuximab. The researchers showed that this strategy generated a clinically meaningful overall response rate to third-line therapy of approximately 20%.

This study also demonstrated that patients who did not have *RAS* or *BRAF* mutations at the time of rechallenge tended to respond much better to treatment than those who still had these mutations. This study was one of the first to support the use of liquid biopsies to determine mutational status at the time of rechallenge.

Many subsequent studies followed suit in using liquid biopsy at the time of EGFR rechallenge, including E-Rechallenge from Japan[3,4] and CHRONOS.[5] Ongoing studies include REMARRY and PURSUIT, both of which are single-arm phase 2 studies.[6] Patients who are *RAS/BRAF*–wild-type are enrolled in REMARRY, which is the monitoring phase of the study with liquid biopsies, and those who progress but have an absence of resistance mutations are enrolled in PURSUIT, which is the anti-EGFR rechallenge portion of the study. What all these studies have shown or are attempting to show is the viability of anti-EGFR rechallenge in the absence of resistance mutations by liquid biopsy at the time of rechallenge.

One of the first findings from this constellation of studies is that those who are *RAS/BRAF*–wild-type and have the absence of resistance mutations tend to respond best to anti-EGFR rechallenge.

H&O Do any other factors affect which patients are most likely to respond to EGFR inhibitor rechallenge?

JG One of the first findings from this constellation of studies is that those who are *RAS/BRAF*–wild-type and have the absence of resistance mutations tend to respond best to anti-EGFR rechallenge. These studies also suggest that the patients who are most likely to benefit from a rechallenge strategy are those who experienced a complete response, partial response, or stable disease for at least 6 months with first-line anti-EGFR therapy. Another finding is that patients who have a longer interval between first-line and third-line anti-EGFR–based therapy are more likely to experience a response to EGFR rechallenge.

H&O What additional studies have been conducted or are ongoing?

JG The phase 2 VELO study, which was recently published in *JAMA Oncology*, is important because it was one of the first randomized studies to examine anti-EGFR rechallenge.[7] In this study, 62 patients who had completed second-line therapy without an anti-EGFR agent were randomly assigned in a 1:1 ratio to receive the anti-EGFR agent panitumumab plus trifluridine/tipiracil or trifluridine/tipiracil alone. The researchers found that the median PFS was significantly higher in the panitumumab group than in the control group, at 4.0 vs 2.5 months (hazard ratio, 0.48; 95% CI, 0.28-0.82; *P*=.007). Liquid biopsy showed that patients without resistance mutations responded better to the anti-EGFR rechallenge strategy.

In addition, there is the ongoing FIRE-4 study, which is one of the few phase 3 randomized studies on anti-EGFR rechallenge.[8] All patients in this ongoing study receive first-line treatment with FOLFIRI plus cetuximab. After that, patients in arm A continue to receive FOLFIRI/cetuximab until progression or intolerable toxicity, and those in arm B receive FOLFIRI/cetuximab for 8 to 12 cycles, followed by maintenance therapy with 5-FU/leucovorin plus bevacizumab. Second-line therapy will not include an anti-EGFR agent, and third-line therapy will be an anti-EGFR–based therapy. Liquid biopsies will be conducted at multiple points of the study. This is one of the few randomized phase 3 trials in this area of anti-EGFR rechallenge.

H&O What other agents are best to pair with anti-EGFR agents as third-line therapy?

JG Historically, we would pair anti-EGFR agents with a chemotherapy backbone. However, more recent trials are investigating novel combinations with anti-EGFR agents. For example, the phase 2, single-arm CAVE study investigated anti-EGFR rechallenge in combination with the immune checkpoint inhibitor avelumab (Bavencio, EMD Serono/Pfizer).[9] That study showed a median overall survival of approximately 11 months, leading to the phase 2, randomized CAVE-2 study. In this ongoing study, a total of 173 patients will be randomized in a 2:1 ratio to cetuximab/avelumab or single-agent cetuximab (NCT05291156). It will be interesting to see whether a nonchemotherapy partner such as immune checkpoint inhibition can improve results.

Disclosures

Dr Gong has served as a consultant or advisor to EMD Serono, Elsevier, Exelixis, QED Therapeutics, Natera, Basilea, HalioDx, Eisai, Janssen, Astellas, and Amgen.

Suggested Readings

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